IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Timothy J. Barberich and James W. Young

Applicant's Docket No.: SPC89-05 Group Art Unit: 1205

Filed: Examiner:

Title: METHOD FOR TREATING ASTHMA USING OPTICALLY PURE R(-) ALBUTEROL

To: Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

PRELIMINARY REMARKS

Dear Sir:

This application is a file wrapper continuation of our earlier application, serial number 07/896,725 which is itself a continuation of application serial number 07/461,262.

Status of Claims

Claims 1 to 12 were presented in the '262 case as originally filed. Claims 7, 10, 11 and 12 were canceled and claims 13 and 14 were added in the response of September 23, 1991 in the '262 case. Claims 9, 13 and 14 were canceled and claims 15, 16, 17 and 18 were presented in the response of February 10, 1993 in the '725 case. Claims 1 to 6, 8 and 15 to 18 are therefore presently pending in the application. Three of these are independent claims (claims 1, 6 and 15).

All of the claims were rejected in the final action of June 7, 1993 (paper number 26) and the rejection was maintained in two subsequent advisory actions (papers 30 and 32). Thus, the status of the claims at the end of prosecution in the parent ('725) case was as follows:

| Allowed Claims | Claims Objected To | Claims Rejected |
|---|---|---|
| None | None | 1 to 6, 8, 15 to 18 |

## Status of Amendments

An amendment was proffered in applicants' response of July 23, 1993, but it was not entered. The amendment is not believed necessary for further prosecution and has not been subsequently presented.

## Summary of the Invention

Applicants' invention is directed to a method of treating asthma and reducing the undesirable side effects associated with racemic albuterol by using the R isomer of albuterol substantially free of the S isomer. R-albuterol may be combined with a bronchodilator, antihistamine or analgesic. Methods and pharmaceutical compositions relating to the combination also fall within the inventive concept.

The administration of $\beta$-agonists for the treatment of asthma is commonly accompanied by undesirable side effects. Evidence suggests that $\beta_2$-agonists may make asthma worse, perhaps by increasing airway hyperresponsiveness to spasmogens. This gives rise to the most serious of the side effects associated with the use of $\beta$-agonists to treat asthma: death from asthma. In this regard, Spitzer et al. [New England Journal of Medicine 326, 501-506 (1992)] have shown that racemic albuterol, taken by metered dose inhaler, was associated with an increased risk of death from asthma or near fatal asthma. When the odds ratio was calculated with adjustment for all factors, the increase in risk (to an odds ratio of 2.8) was clinically important and statistically significant.

Applicants have surprisingly found that, with regard to hypersensitivity, there is an unexpected advantage to the use of the pure R isomer. Applicants have shown (see the declaration of Gunnar Aberg accompanying the response of July 23, 1993) that the S isomer causes a hypersensitivity to allergen and that the desired bronchodilator effect due to the R isomer is prone to tachyphylaxis (desensitization), whereas

the undesired hypersensitivity arising from the S isomer is less prone to tachyphylaxis. This means that, in order to achieve bronchodilation, a patient in chronic treatment requires ever-increasing doses of racemic albuterol. While greater and greater doses of R-albuterol are needed to provide the desired bronchodilation, the accompanying greater and greater doses of S-albuterol dramatically increase the patient's susceptibility to asthmatic attack. Similar results have appeared, subsequent to applicants' invention, in two independent publications from other labs [Morley et al., British Journal of Pharmacology, 104, Supplement, 295P (1991) and Chapman, et al. Tran. In Pharm. Science 13, 231-232 (1992)]. Thus, by eliminating the S-isomer and its undesirable hypersensitization, applicants have found an unexpected benefit to the use of the pure R isomer for the treatment of asthma.

## Issues

1. In the office action of June 7, 1993, a final rejection in the parent case, the examiner rejected claims 1 to 6 and 15 to 18 over Chemical Abstracts 89:123259m for "reasons of record." The reasons of record are found in the office action of August 20, 1990, in which the examiner states that the reference teaches the use of albuterol to treat asthma and that it is his position that the determination of a particular isomer to employ would be a matter of obvious alternatives to one skilled in the art.

2. The examiner also rejected claims 1 to 5 as unpatentable under 35 U.S.C. §103 over Brittain et al. [Brit. J. Pharmacol. 48, 144-147 (1973)], Hartley et al. [J. Med. Chem. 14, 895 (1971)] and Buckner et al. [JPET 189, 616-625 (1974)]. These references are relied upon to teach "the greater bronchodilation activity of the R isomer over the S isomer."

3. Claims 6, 8 and 15 to 18 were rejected under 35 U.S.C. §103 as obvious over Brittain et al, Hartley et al, and

Buckner et al, as before and further in view of Chemical Abstracts "for reasons of record." There is no "record" with regard to claims 15 to 18, which were newly presented in the response immediately preceding the rejection. One assumes from analogy to earlier office actions that the examiner takes the position that the Brittain, Hartley and Buckner references teach greater bronchodilation activity of the R isomer, and that the Chemical Abstracts reference teaches albuterol in combination with other drugs.

4. The examiner's position is that the declaration under 37 C.F.R. 1.132 of Gunnar Aberg of July 23, 1993 "failed to show unexpected activity or less undesirable side effects (e.g. comparative therapeutic indices)."

5. The examiner cited the case of *In re Adamson* [125 USPQ 233] for the proposition that a showing of unexpected activity in a Rule 132 declaration might not overcome his obviousness rejection.

Argument

Issue 1 - The rejection of claims 1 to 6 and 15 to 18 over Chemical Abstracts 89:123259m.

The Chemical Abstracts reference is directed to a comparison of bronchodilator effects of racemic albuterol and drug combinations incorporating racemic albuterol. The reference does not teach or suggest the use of an optically pure isomer of albuterol either alone or in combination. Arguably, the reference teaches away from the use of a single isomer to reduce side effects: it states, "a combination of salbutamol [albuterol] and hydroxyzine seems, therefore, to be one rational means of treating asthma with fewer side effects than the salbutamol-hydroxyzine-theophylline mixture, but still about the same effectiveness." Thus, the goal of the reference appears to be to lower the side effects associated with albuterol. However, rather than separate the enantiomers and use one enantiomer, as taught by applicants, (which the

examiner has alleged would be obvious) the authors turned instead to modulating components of the mixture.

The examiner's position that "the determination of a particular isomer to employ would be a matter of obvious alternatives" is only true if it is obvious that the use of a single isomer provides an advantage. That teaching is entirely missing from the reference. In this regard, it is worth noting that the mere fact that enantiomers exist does not render the use of a particular enantiomer obvious. In order to use an enantiomer, one must first prepare or isolate the single pure enantiomer. Because chemical resolution of a racemic mixture is never 100% efficient, a resolution will always yield less than 50% of the single isomer. Chiral syntheses are similarly expensive and/or inefficient. As stated by others (e.g., European patent application 256586, page 2, line 8) "a major reason for the continued use of mixtures of stereoisomers is that the cost of separation of the stereoisomers exceeds the potential advantage of a possible increase in activity." It would not have been obvious to prepare and use optically pure R-albuterol because there is no suggestion of any advantage of R-albuterol in the reference.

Issue 2 - The rejection of claims 1 to 5 as obvious over Brittain et al., Hartley et al. and Buckner et al.

Brittain et al. show that both enantiomers and the racemic mixture of albuterol are very selective for $\beta_2$ receptors, but the isomeric activity ratio of R- and S-albuterol on isolated tracheal muscle ($\beta_2$) vs atrial muscle ($\beta_1$) is "impossible to calculate...because the isomers are virtually inactive on this tissue." The potency ratio of R(-) vs racemic albuterol in $\beta_2$ receptors as measured by acetylcholine-induced bronchospasm in anesthetized guinea pigs is 1.28, in acetylcholine-induced pulmonary resistance in anesthetized dogs is 2.3 and on isolated guinea pig trachea is

0.90 (i.e. the racemate is 1.1 times as potent as the R isomer). Thus, from a study of the Brittain reference one may conclude nothing definitive regarding either the selectivity of R vs racemic or of the potency of R vs racemic.

Hartley and Middlemiss teach that both isomers and the racemic mixture of albuterol act on $\beta_2$ receptors rather than $\beta_1$ receptors. The effects of the R isomer and the racemic mixture are equiactive on $\beta_2$ receptors of the intact guinea pig trachea and indeed the racemate is reported to be 1.5 times as potent as the R isomer. There is no clear teaching with regard to selectivity between $\beta_1$ and $\beta_2$-receptors, which might indicate the potential for side effects. Thus no conclusion can be drawn from Hartley and Middlemiss as to whether the R isomer would enjoy any advantage over racemic albuterol in terms of side effects.

The study by Buckner and Abel examines the ratio of activity of the R and S isomers of albuterol in guinea pig atria and guinea pig trachea. They concluded "even though the potencies of single isomers may differ as much as twenty-four fold between atria and trachea, the stereoselectivity for production of activity is the same." That is, the selectivity, as measured by the ratio of tracheal to atrial activity, is the same for the two isomers. Buckner did not examine racemic albuterol, so no conclusion can be drawn as regards any potency advantage of a single pure R isomer vs the racemate.

In an earlier office action (December 9, 1991) the examiner had rejected the same claims over an additional reference by Hawkins et al. [J. Med. Chem. 16, 856-857 (1973)]. Although the rejection over Hawkins was not maintained in the final office action, it appears pertinent to the substance of the rejection, which might otherwise lack a balanced consideration of the art. In their studies, Hawkins et al. found that the R enantiomer was 2.15 times as potent as the racemate. They did not examine any tissue other than guinea pig trachea so that no conclusion relating to relative

selectivity could be drawn.

The issue of patentability must be approached "in terms of what would have been obvious to one of ordinary skill in the art at the time the invention was made in view of the sum of all of the relevant teachings in the art ..." [*In re Kuderna* (165 USPQ 575)]. There are two teachings that could have rendered the use of R-albuterol obvious: (1) a teaching that it is more than twice as potent as the racemate (which would indicate that the S-isomer's activity is antagonistic to the R-isomer's potency); or (2) a teaching that fewer side effects are associated with the R isomer. Neither of these teachings is found in any of the references. However, the art is not silent on what the person of skill ought to expect; it teaches that there is nothing to be gained, either in potency or side effects, by resolving the racemic albuterol. Hawkins et al. and Buckner et al. appear to indicate that the R isomer is about twice as potent as the racemate (which merely indicates that the S-isomer is inert); Hartley et al. teaches that the racemate is about 1.5 times as potent as the R isomer (which would indicate that the S-isomer has some therapeutic potency); Brittain et al. indicates that one or the other isomer is more potent, depending on the test. There is a certain lack of agreement among the references concerning the relative potency of the R isomer and the racemate, and the person of ordinary skill in the art would be, at least, confused by the cited references.

If one ignores some of the references, it appears that the R isomer may enjoy a theoretical twofold potency advantage over the racemate. However, even assuming that R-albuterol is twice as potent as the racemate, this would not motivate a person of skill and experience in the pharmaceutical industry to prepare and administer the pure R isomer. This is because, as discussed above, a process for the resolution of racemic albuterol would inevitably produce R-albuterol in less than 50% yield, whereas assuming that S-albuterol is totally inert ballast, the use of the racemic albuterol would, at worst,

provide 50% of the potency of the pure R. Thus there is nothing to be gained by resolving the racemate. A potency ratio significantly greater than two between a single enantiomer and its racemate would be consistent with antagonism by one enantiomer and would provide motivation for resolving the racemate. However, no such teaching is found in any of the references, even when viewed selectively. Therefore at the time of filing, the art did not, on the basis of potency, suggest any practical advantage to using pure R albuterol.

A second basis for separating enantiomers would be to provide lessened side effects. Indeed, the unexpected diminution in side effects when the pure R isomer of albuterol is administered is the basis of the instant application, but it is not suggested by any of the references. As explained in the July 23, 1993 declaration of Gunnar Aberg, side effects of drugs that have a predominant $\beta_2$ agonist component can arise from four presently recognized interactions: (a) non-adrenergic effects; (b) interaction of the $\beta$-agonist with $\alpha$-receptors; (c) interaction of the $\beta_2$ agonist with $\beta_1$ receptors; and (d) interaction of the $\beta_2$ agonist with $\beta_2$ receptors.

(a) Non-adrenergic effects can be triggered by interaction with any of the hundreds of other receptors and by non-receptor interactions, and they can originate from portions of the drug molecule outside the $\beta_2$ pharmacophore. They are, for this reason, difficult to predict or screen for. Applicants are aware of no teachings in the literature of relative liabilities of racemate or enantiomers of albuterol as regards non-adrenergic effects, and theoretically such differences would be improbable.

(b) Interaction of $\beta$-agonists with $\alpha$-receptors are known in first generation adrenergics but are not generally of clinical significance in second generation agonists like albuterol. Likewise,

applicants are aware of no art that would suggest any distinction between racemate and enantiomers on this basis.

(c) The interaction of $\beta_2$ agonists with $\beta_1$ receptors, causing pulmonary agents to exhibit cardiac side effects, is well documented and has been discussed above for Brittain, Hartley, Buckner and Hawkins. The literature cited provides no evidence for an advantage of either enantiomer of albuterol on the basis of $\beta_1$ vs. $\beta_2$ specificity.

(d) The fourth interaction, $\beta_2$ agonists acting at $\beta_2$ receptors giving rise to tachyphylaxis and sensitization, is known but not described in any of the references cited for albuterol.

Thus, in January of 1990 when the grandparent of the present application was filed, there was no teaching in the art that the use of pure R-albuterol enjoyed any advantage in diminution of side effects.

Issue 3 - The rejection of claims 6, 8 and 15 to 18 over Brittain et al, Hartley et al, Buckner et al and Chemical Abstracts.

The inadequacy of Brittain, Hartley and Buckner to support the rejection of applicants' claims to the use of R-albuterol has been presented above. The addition of the Chemical Abstracts reference, while indicating that racemic albuterol has been used with other drugs, does not supply the missing teaching regarding the advantage of the use of the R isomer in diminishing side effects.

Issue 4 - The setting aside of the Declaration of Dr. Gunnar Aberg.

Accompanying the response of July 23, 1993, applicants provided a declaration from Dr. Gunnar Aberg to establish that

his results and those of Chapman and of Morley would indicate to the person of skill in the art that the R isomer would have a higher therapeutic index in humans than would the racemate. Dr. Aberg averred that the tests relied on as evidence are accepted in the art as being predictive of efficacy in treating humans; the pending method of use claims are narrowly drawn to the specific use for which the tests are predictive. [See Ex parte Chwang (231 USPQ 751).] Dr. Aberg's credentials were presented in the declaration and his conclusions as to side effects and unexpected activity cannot be set aside by the examiner without some basis for so doing. None was presented. Therefore it is presumed that the declaration is accepted for what it teaches; namely, that a person of skill in the art would accept the studies in guinea pig trachea and the experiments of Chapman et al. and Morley et al. (described below) as predictive of a higher therapeutic index for R-albuterol. Applicants believe that the examiner's position that the declaration "failed to show unexpected activity or less undesirable side effects" cannot be maintained.

Dr. Aberg described experiments carried out in his laboratory in which isolated tracheal muscle preparations were subjected to graded doses of a spasmogen. It was found that the contractile response to the spasmogen was significantly increased in bronchial tissue strips that had been incubated with S-albuterol. No such effect was seen in the tissues that had been incubated with R-albuterol. Dr. Aberg concluded that the increased sensitivity to spasmogens from treatment with S-albuterol was due to a direct effect on bronchial smooth muscle.

Subsequent to the filing of applicants' original application, Morley et al. (op. cit.) and Chapman et al. (op. cit.) independently disclosed that the S isomer in bronchial tissue causes a hypersensitivity to allergen. Chapman et al. stated, "It has long been recognized that the use of sympathomimetics for asthma therapy is associated with a range

of inconsistent or frankly paradoxical effects...our findings indicate that it may be prudent to remove enantiomers **that were previously thought to be biologically inert."** Thus Morley and Chapman came to the same conclusion as applicants' original disclosure, and did so with the same understanding of the prior art as a whole: namely, that no expectation of an improved side effect profile was previously attached to the use of a single enantiomer.

In the period since the final office action of June 7, 1993 in the parent case, additional support for the conclusions drawn in the Aberg declaration has come to the attention of applicants. British patent application 2,255,503, filed more than a year after applicants' '262 application, discloses that the long standing problems inherent in therapy with albuterol and other $\beta_2$ sympathomimetic bronchodilators may unexpectedly be ameliorated by the expedient of administering the drug not, as hitherto, in the form of a racemic mixture, but as the R isomer (page 8, line 25 to line 33 of the copy enclosed). The problems that may be avoided are enumerated on page 12. A series of experiments is disclosed at page 15 to page 16 in which guinea pigs were challenged with intravenous histamine after intravenous infusion of S-albuterol or vehicle. The results indicated a profound hypersensitivity induced by S-albuterol. The British application comes to the same conclusion as did Dr. Aberg in his declaration: subjects receiving R-albuterol will exhibit a lessened tendency to hyperreactivity with equivalent benefit in terms of bronchodilator action (see page 24, line 3 to line 8 of GB 2,255,503).

This evidence of unexpected activity cannot, as a matter of law, be disregarded by the examiner. [*In re Merck*, 231 USPQ 375, 380 (Fed. Cir. 1986)]

Issue 5 - The applicability of the decision *In re Adamson*.

In the office action of June 7, 1993, the examiner indicated that <u>no</u> showing (even if applicants have made one)

would be persuasive in view of the decision *In re Adamson*. Although *In re Adamson* teaches that optical isomers *per se* are normally obvious over the corresponding known racemate, the decision should not be extended to stand for the proposition that a new method for using an isomer is unpatentable, particularly where, as here, the method unexpectedly provides an improved therapeutic ratio. For example, the claims of U.S. patent 4,851,444 (to Sunshine et al.) cover a method for using S-(+)-ibuprofen for onset-hastened analgesia, although (S)-ibuprofen *per se* was well known at the time of filing the application for a new use.

In *Adamson*, the CCPA held that in establishing that one isomer was more potent, the applicants had "done no more than what is suggested by the prior art and have ascertained no more than what would be expected by one skilled in the art" [Emphasis added]. Applicants' showing goes far beyond the evidence of enhanced potency at issue in *Adamson*. In the present case, applicants have shown that the resolution of the racemate and the use of R-(-)-albuterol substantially free of its S-isomer would provide therapy for asthma while simultaneously reducing side effects. As explained above, this is not suggested by the prior art. To the contrary, the art suggests that there would be no reduction in side effects. Thus, the decision in *Adamson* has no bearing on the patentability of this application.

Respectfully submitted,

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